Respiratory Medicine 114 (2016) 84–90

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

The bronchodilator effects of extrafine glycopyrronium added to combination treatment with beclometasone dipropionate plus formoterol in COPD: A randomised crossover study (the TRIDENT study)

Dave Singh [a, *], Winfried Schröder-Babo [b], Géraldine Cohuet [c], Annamaria Muraro [d], Françoise Bonnet-Gonod [c], Stefano Petruzzelli [d], Martin Hoffmann [e], Zenon Siergiejko [f], on behalf of the TRIDENT study investigators

[a] University of Manchester, Medicines Evaluation Unit, Manchester, UK
[b] Pulmonology Department, Gelnhausen, Germany
[c] Global Clinical Development, Chiesi S.A., Paris, France
[d] Global Clinical Development, Chiesi Farmaceutici S.p.A., Parma, Italy
[e] Pneumologicum, Practice for Internal Medicine and Pneumology, Hannover, Germany
[f] Respiratory System Diagnostics and Bronchoscopy Department of Medical University in Bialystok, Poland and Private Practice Internal Medicine and Allergology, Bialystok, Poland

ARTICLE INFO

Article history:
Received 4 January 2016
Received in revised form
23 March 2016
Accepted 24 March 2016
Available online 26 March 2016

Keywords:
Bronchodilators
COPD
Triple therapy
Extrafine

ABSTRACT

This multicentre, double-blind, randomised, placebo-controlled, crossover study aimed to determine the dose-response of the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide (GB) when added to beclometasone dipropionate plus formoterol fumarate (BDP/FF) in patients with COPD.

Patients received extrafine GB 12.5, 25 or 50 μg twice daily (BID) or placebo for 7 days via pressurised metered dose inhaler (pMDI), and extrafine BDP/FF via pMDI throughout the study. The primary objective was to demonstrate superiority of GB plus BDP/FF versus BDP/FF in terms of FEV_1 area under the curve from 0 to 12 h (AUC_{0-12h}) on Day 7. Secondary endpoints included: FEV_1 AUC_{0-12h} on Day 1; peak FEV_1 and FVC on Days 1 and 7; and trough (12 h post-dose) FEV_1, FVC and inspiratory capacity (IC) on Days 1 and 7.

Of 178 patients randomised (mean age 62.7 years, post-bronchodilator FEV_1 48.9%), 172 (96.6%) completed. Mean FEV_1 AUC_{0-12h} on Day 7 was significantly higher ($p < 0.001$) for all GB doses plus BDP/FF compared to BDP/FF alone, with the difference for the 25 and 50 μg BID doses being clinically relevant (i.e., ≥100 mL). The results for the other spirometry endpoints were consistent with the primary endpoint. Adverse events were reported in 7.4, 5.7 and 8.0% of patients receiving GB 12.5, 25 and 50 μg BID, respectively, versus 11.0% of patients receiving BDP/FF alone.

This study confirms the value of adding GB to BDP/FF to improve lung function in COPD patients. The dose of extrafine GB 25 μg BID was associated with the best efficacy/safety profile.

Trial registered at: ClinicalTrials.gov.
Registration number: NCT01476813.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation, with bronchodilators (particularly long-acting) being central to disease management [1]. There are two classes of inhaled long-acting bronchodilators: β_2-agonists (LABAs) and muscarinic antagonists (LAMAs). Long-acting bronchodilators improve lung function, alleviate symptoms, increase exercise performance and reduce exacerbation rates [1,2], and are recommended for use in patients who are symptomatic despite

* Corresponding author.
E-mail address: dsingh@meu.org.uk (D. Singh).

http://dx.doi.org/10.1016/j.rmed.2016.03.018

short acting bronchodilator treatment. Inhaled corticosteroids (ICSs) are used in combination with LABAs in those patients who are at increased risk of exacerbations [1], and such ICS/LABA combinations have been shown to reduce the rate of exacerbations and improve a range of clinically-relevant outcomes compared with ICS or LABA monotherapy [3,4].

Foster® (Chiesi Farmaceutici S.p.A., Parma, Italy) is an extrafine formulation fixed-dose combination (FDC) of the ICS beclometasone dipropionate (BDP) and the LABA formoterol fumarate (FF) delivered via a hydrofluoroalkane (HFA) pressurised metered dose inhaler (pMDI). A 48-week study in COPD patients showed that BDP/FF was superior to FF monotherapy in terms of the rate of exacerbations, lung function and health-related quality of life [4]. Other studies have shown similar clinical benefits with BDP/FF compared to other ICS/LABA FDC commonly used in clinical practice, namely fluticasone propionate/salmeterol and budesonide/formoterol [5,6].

A triple therapy regimen of LABA, LAMA and ICS is a recognised treatment strategy for COPD patients who have a high burden of symptoms and who are at increased risk of exacerbations; these patients are categorised as GOLD category D [1]. In clinical practice it is common for patients with COPD to be 'stepped up' from mono-LAMA or ICS/LABA therapy to such a triple regimen [7], and there is evidence that stepping up treatment in this manner provides significant and clinically important patient benefits such as improved symptoms and reduced exacerbation rates [8,9].

An extrafine formulation of the LAMA glycopyrronium bromide (GB) is in clinical development to be combined with BDP/FF in a single inhaler (a 'fixed triple') for the management of COPD. The aim of this study was to determine the dose-response effects of GB in COPD patients on background BDP/FF treatment. An important aspect of the study design was that we included only patients who were being treated with ICS/LABA FDCs on entry to the study.

2. Materials and methods

2.1. Participants

This was a multicentre, double-blind, randomised, active- and placebo-controlled, 4-way crossover study, that recruited males and females from 40 to 80 years of age, who had a diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document. To be eligible, patients were required to have a post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio <0.7, a post-bronchodilator FEV_1 between 30 and 60% of the predicted value, and an increase in FEV_1 of at least 60 mL at 30 min after inhalation of 80 μg ipratropium. All patients were to be receiving an ICS/LABA combination on entry to the study (ICS/LABA plus tiotropium was acceptable providing this was taken for no longer than 1 month prior to study entry; tiotropium was not to be taken from 24 h prior to screening and for the duration of the study). Current or ex-smokers with a smoking history of at least 10 pack-years were eligible.

The key exclusion criteria were: a diagnosis of asthma, or history of allergic rhinitis or atopy; hospitalisation for COPD or pneumonia within 3 months prior to screening; a COPD exacerbation requiring systemic steroids and/or antibiotics in the 4 weeks prior to screening, or during the run-in period; and hypersensitivity to any of the study drugs or excipients. Patients were also excluded if they had clinically significant abnormal electrocardiograms (ECG), QTc (Fridericia's formula) > 450 ms for males or >470 ms for females, clinically significant laboratory abnormalities that could impact the feasibility of the results, or unstable concurrent disease, or required long-term (at least 12 h daily) oxygen therapy for chronic hypoxaemia.

2.2. Trial design

The study was conducted at a mixture of primary, secondary and tertiary care, and specialised research institutions. It comprised four 7-day treatment periods with 7-day washout periods between treatments (Fig. 1). At the screening visit (Visit 1), inclusion and exclusion criteria were checked, with spirometry assessed pre- and 30-min post ipratropium 80 μg. There was a 4-week run-in period between Visits 1 and 2, during which all patients received BDP/FF 100/6 μg, two inhalations (i.e., 200/12 μg) twice daily (BID) via pressurised metered dose inhaler (pMDI). At the baseline visit (Visit 2), after confirming eligibility, patients were randomised equally to one of four treatment sequences. On Day 1 of each treatment period (Visits 2, 4, 6 and 8), pre- and post-dose spirometry (FEV_1, FVC and inspiratory capacity [IC]) were measured (at −45, −10, 15, 30 and 45 min, and 1, 2, 4, 6, 8, 10 and 12 h, and 12 h 30 min). The evening dose of study medication was inhaled after the 12 h 30 min spirometry assessments. On Day 7 of each treatment period (Visits 3, 5, 7 and 9), pre- and post-dose spirometry (FEV_1, FVC and IC) were measured at the same timepoints as Day 1, and also at 14 h, 23 h 30 min and 24 h. As with the Day 1 visit, the evening dose of study medication was inhaled after the 12 h 30 min spirometry assessments, and so the 14 h, 23 h 30 min and 24 h spirometry assessments were therefore effectively obtained at 1 h 30 min, 11 h and 11 h 30 min after the evening dose of medication.

The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the Independent Ethics Committees or Independent Review Boards at all sites prior to initiation. All patients provided written informed consent at a prescreening visit before any study procedure was performed. There were no amendments to the protocol.

2.3. Interventions

Over the four treatment periods, patients were to receive GB 12.5, 25 and 50 μg BID (i.e., total daily doses of 25, 50 or 100 μg), and matching placebo, delivered via HFA pMDI. All patients also received BDP/FF 200/12 μg BID via HFA pMDI for the duration of the study (including the run-in, treatment and washout periods).

Patients were randomised to one of four treatment sequences using a balanced block randomisation scheme generated by Bilcare Global Clinical Supplies, Phoenixville, PA, USA. Patient numbers were centrally assigned via interactive response technology (voice and/or web), with treatment kits corresponding to the treatment regimen dispensed at the start of each treatment period. All study site personnel and employees of the sponsor (and their representatives) were blinded to treatment, as were the patients.

2.4. Outcomes and assessments

The primary objective was to evaluate the effect of GB 12.5, 25 and 50 μg BID (i.e., total daily doses of 25, 50 and 100 μg) plus BDP/FF compared with BDP/FF alone in terms of FEV_1 time-normalised area under the curve from 0 to 12 h (AUC_{0-12h}) on Day 7. Secondary objectives included the evaluation of GB plus BDP/FF compared with BDP/FF alone in terms of: FEV_1 AUC_{0-12h} on Day 1; peak FEV_1 and FVC on Days 1 and 7; trough FEV_1, FVC and IC at 12 h on Days 1 and 7 (where trough was the mean of the assessments at 12 and 12.5 h post-dose); trough FEV_1, FVC and IC assessed on the morning of Day 8 (the mean of the assessments at 23.5 h and 24 h after the time of dosing on the morning of Day 7); individual timepoint FEV_1, FVC and IC on Days 1 and 7; and rescue medication use across the

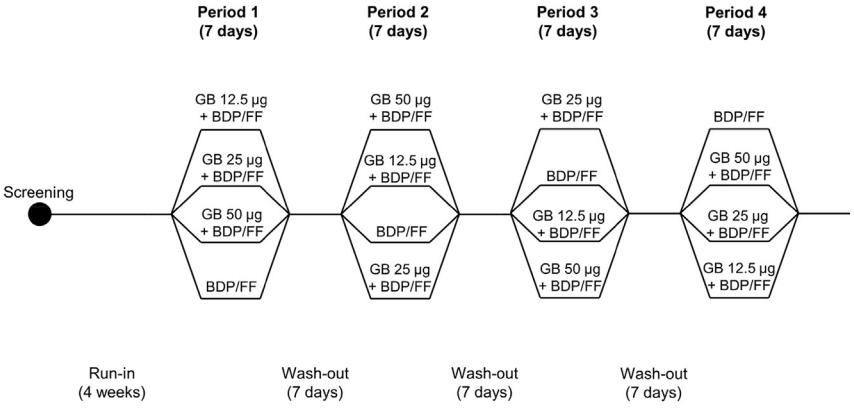

Fig. 1. Study design.

treatment period (puffs per day, percentage of days with no use, and average number of times that rescue medication was used). Safety was assessed in terms of adverse events (AEs) and serious adverse events (SAEs), together with vital signs in each treatment period. Treatment compliance was evaluated on the basis of diary card information recorded daily by patients, calculated as the total number of administered doses divided by the total number of scheduled doses times 100.

2.5. Sample size and statistical methods

A total of 142 evaluable patients would provide 93% power to detect a mean difference of 0.08 L between each dose of GB plus BDP/FF versus BDP/FF alone at a two-sided significance level of 0.01667, assuming a within-subject SD of 0.172 L. Bonferroni's adjustment was used to control the family-wise Type I error rate at 0.05 (two sided). Jointly considering the tests at the three dose levels, the overall study power was 80%. Assuming a non-evaluable rate of 20%, a total of 180 patients would have needed to be randomised. Anticipating a screen failure rate of 30%, a total of 258 patients were required to be screened. Patients who prematurely withdrew from the study were not replaced.

The primary efficacy variable, FEV_1 AUC_{0-12h}, was calculated based on actual times using the linear trapezoidal rule. The results were then analysed using an analysis of covariance (ANCOVA) model, with treatment, period and patient as fixed effects and baseline FEV_1 (mean of the 45 min and 10 min predose on Day 1 values) as covariate. Adjusted mean differences were calculated, together with Dunnett's simultaneous 95% confidence intervals (CIs) and p values.

Secondary FEV_1, FVC and IC variables were analysed using a similar ANCOVA model as used for the primary variable, using baseline FEV_1, FVC or IC, as relevant. Peak FEV_1 and FVC values were the maximum obtained between 15 min and 12.5 h post-dose. Mean individual timepoint FEV_1, FVC and IC were summarised by treatment. The rescue medication variables were analysed using an analysis of variance (ANOVA) model, with treatment, period and patient as fixed effects. AEs and SAEs are presented descriptively.

The intent-to-treat (ITT) population comprised all patients who received at least one administration of study medication and had at least one post-baseline efficacy evaluation. The per-protocol (PP) population, which was used only for the primary efficacy variable, comprised all patients in the ITT population without any major protocol deviations. The safety population comprised all patients who received at least one administration of study medication.

3. Results

3.1. Participants

The study started in March 2012, and the last patient completed in September 2012. The study was conducted at 31 centres (4 primary care, 17 secondary or tertiary care, and 10 specialist research institutions): 10 in Germany, 6 in Hungary, 2 in Italy, 5 in Poland, 6 in Russia and 2 in the United Kingdom. Of 255 patients screened, 178 were randomised; the majority of patients (n = 172; 96.6%) completed the study. Of the 77 patients who were not randomised, 65 did not meet the lung function inclusion criteria. Three patients (1.7%) prematurely discontinued due to withdrawal of consent, and 3 (1.7%) due to adverse events. Baseline demographics and disease characteristics are shown in Table 1. Demographic and disease characteristics of the 77 patients who were not randomised were similar to the overall randomised population: 42 (64.5%) were male; mean age 62.2 years; mean FEV_1 post-ipratropium 55.6% (22.0–81.0%); mean reversibility to ipratropium 7.5%.

The majority of patients (n = 174; 97.8%) were receiving ICS/LABA combination for their COPD on entry to the study; the remainder (n = 4; 2.2%) were receiving triple therapy. Compliance to treatment was very high, with a mean of 99.4% of scheduled doses taken during the treatment periods.

Table 1
Patient baseline demographics and disease characteristics (safety population).

	Overall (N = 178)
Male gender, n (%)	119 (66.9)
Race, Caucasian, n (%)	178 (100)
Age, years, mean (SD)	62.7 (7.54)
Body mass index, kg/m^2, mean (SD)	27.0 (5.72)
Smoking status, n (%)	
Ex-smoker	81 (45.5)
Smoker	97 (54.5)
Pack-years, mean (SD)	46.9 (26.13)
Duration of smoking, years, mean (SD)	40.6 (8.90)
Time since COPD diagnosis, years, mean (SD)	8.3 (6.15)
FEV_1, L, mean (SD)[a]	1.41 (0.335)
FEV_1, % predicted, mean (SD)[a]	48.9 (7.34)
30%–<50%, n (%)	81 (45.5)
50%–<60%, n (%)	95 (53.4)
FEV_1 reversibility, %, mean (SD)[b]	16.4 (12.06)
FEV_1 reversibility, mL, mean (SD)[b]	190 (110)
FEV_1/FVC, mean (SD)[a]	0.45 (0.100)
IC, L, mean (SD)[a]	2.21 (0.69)

[a] Post-ipratropium (80 µg).
[b] Post vs pre-ipratropium (80 µg).

3.2. Primary endpoint: FEV_1 $AUC_{0–12h}$ on Day 7

The mean FEV_1 $AUC_{0–12h}$ on Day 7 was significantly higher for all three GB doses plus BDP/FF compared to BDP/FF alone, with differences ranging from 87 mL to 112 mL in the ITT population (Fig. 2), and the difference for the 25 and 50 μg BID doses being clinically relevant (i.e., ≥100 mL [10]). The difference between GB 50 μg BID and 12.5 μg BID reached statistical significance (25 mL, $p = 0.025$); the other comparisons between GB doses were not statistically significant. A similar effect was observed in a *post-hoc* analysis of the subgroup with baseline post-bronchodilator FEV_1 <50% predicted, with differences between GB plus BDP/FF vs BDP/FF alone of 85, 86 and 115 mL for GB 12.5, 25 and 50 μg, respectively ($p < 0.001$ for all GB doses). A further *post-hoc* analysis was conducted to assess the proportion of 'responders', defined as a change in FEV_1 $AUC_{0–12h}$ from baseline to Day 7 of >100 mL. The percentage of patients meeting this definition were: 56.6%, 60.0%, and 65.1% with BDP/FF plus GB 12.5, 25, and 50 μg respectively, and 31.4% with BDP/FF alone.

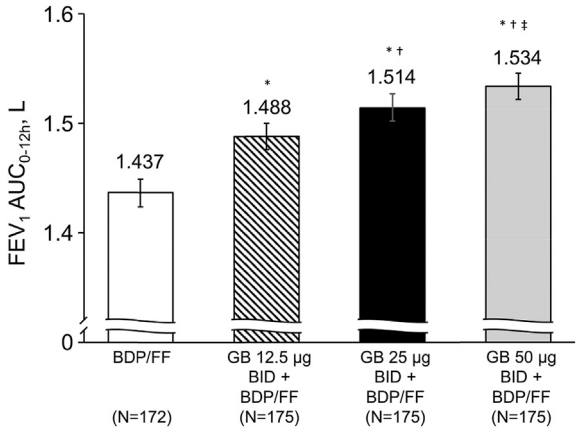

Fig. 3. FEV_1 $AUC_{0–12h}$ on Day 1 (ITT population). (Data are adjusted mean and 95% CI; N values are for the ITT population. *$p < 0.001$ vs BDP/FF; †$p < 0.05$ vs GB 12.5 μg BID plus BDP/FF; ‡$p < 0.05$ vs GB 25 μg BID plus BDP/FF).

3.3. Secondary efficacy endpoints

3.3.1. FEV_1 $AUC_{0–12h}$ on Day 1

The addition of all three GB doses to BDP/FF resulted in statistically significant increases in FEV_1 $AUC_{0–12h}$ on Day 1 (Fig. 3). The 50 μg BID dose was statistically superior to the 25 and 12.5 μg BID doses, and the 25 μg BID dose was statistically superior to the 12.5 μg BID dose.

3.3.2. Trough FEV_1, FVC and IC

Trough FEV_1 at 12 h post-dose on Days 1 and 7, and on the morning of Day 8 (assessed at 24 h after the morning dose on Day 7 – in other words, approximately 11.5 h after the evening dose) are shown in Fig. 4, with the respective FVC and IC data in Supplementary Figs. 1 and 2. As with the primary endpoint, the addition of all three doses of GB was associated with statistically significant improvements compared with BDP/FF alone for trough FEV_1, FVC and IC at all three timepoints, with a trend towards increased efficacy with increased GB dose. The addition of GB 12.5, 25 and 50 μg BID doses resulted in increases vs BDP/FF in trough FEV_1 at 12 h post-dose of 49, 92 and 106 mL, respectively, on Day 1 and 79, 91 and 105 mL, respectively, on Day 7. A *post-hoc* analysis was conducted to assess the proportion of 'responders', defined as a change in trough FEV_1 from baseline to the morning on Day 8 of >100 mL. The percentage of patients meeting this definition were: 37.6%, 42.9%, and 43.0% with BDP/FF plus GB 12.5, 25, and 50 μg, respectively and 19.8% with BDP/FF alone.

3.3.3. Peak FEV_1 and FVC

The peak values for FEV_1 and FVC in the three GB plus BDP/FF groups were significantly higher ($p \leq 0.001$) than the BDP/FF group on both Day 1 and Day 7. On Day 7, the differences in peak FEV_1 between BDP/FF and GB were 83 mL for the 12.5 μg BID dose, 90 mL for the 25 μg BID dose and 101 mL for the 50 μg BID dose.

3.3.4. Other secondary efficacy endpoint data

FEV_1 reached a peak at 2 h post-dose with all treatments on both Day 1 (data not shown) and Day 7 (Fig. 5), with a greater improvement observed at all timepoints in the three GB plus BDP/FF groups compared with the BDP/FF alone group. Similar results

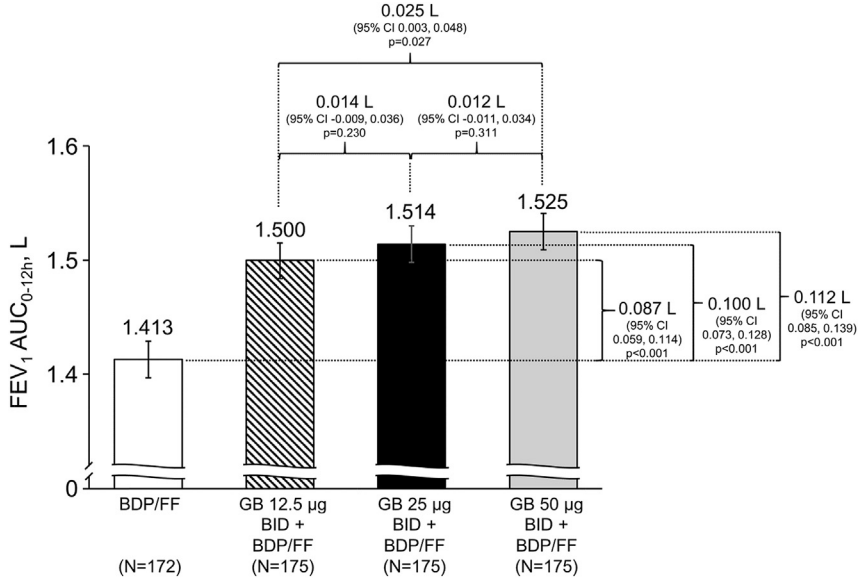

Fig. 2. Primary endpoint – FEV_1 $AUC_{0–12h}$ on Day 7 (ITT population). (Data are adjusted mean and 95% CI; N values are for the ITT population).

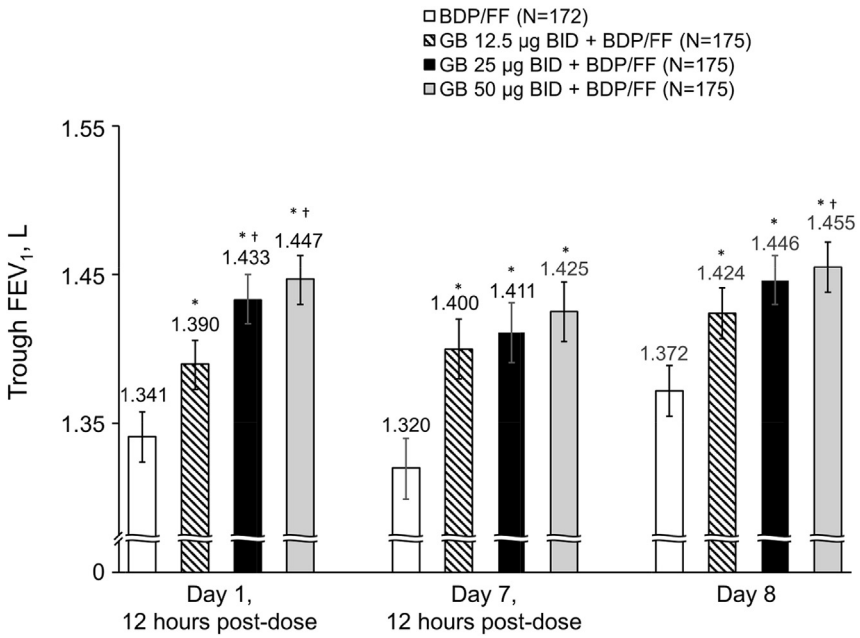

Fig. 4. Trough FEV_1 at 12 h post-dose on Days 1 and 7, and on Day 8 (ITT population). (Data are adjusted mean and 95% CI; N values are for the ITT population. *p < 0.001 vs BDP/FF; †p < 0.05 vs GB 12.5 µg BID plus BDP/FF). Note: This figure shows trough FEV_1 assessed at 12 h after the morning dose on Days 1 and 7, and assessed on the morning of Day 8 at 24 h after the morning dose on Day 7 – in other words, approximately 11.5 h after the Day 7 evening dose.

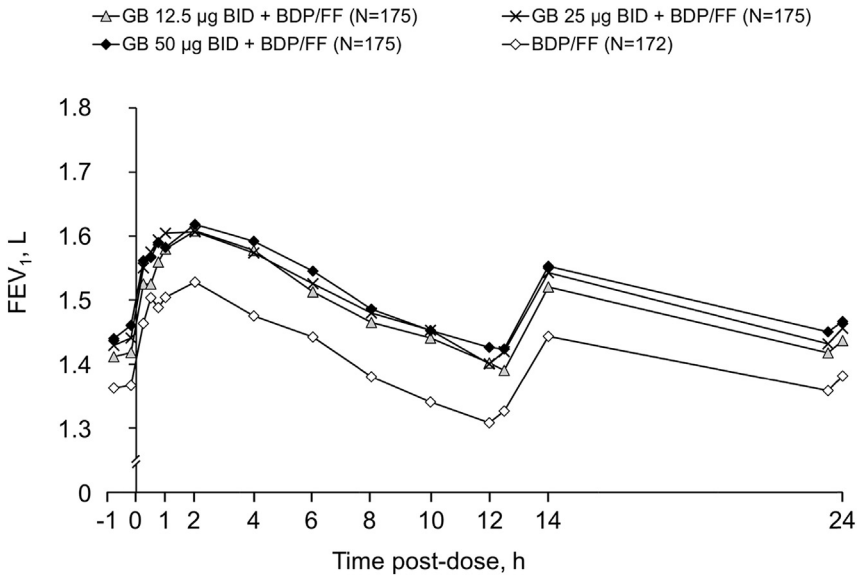

Fig. 5. Individual timepoint FEV_1 on Day 7 (ITT population). (Data are mean; N values are for the ITT population).

were observed for both FVC and IC. Use of rescue medication was similar across groups, with no statistically significant differences in any of the endpoints.

3.4. Safety results

Overall, 70 treatment-emergent AEs were reported in 47 patients, and more frequently in the BDP/FF group than any of the GB plus BDP/FF groups (Table 2). The treatment-emergent AEs occurring in more than one patient in any treatment group were nasopharyngitis, oral herpes, headache, fatigue, and increased blood bilirubin. The majority of AEs were mild in severity; only four were classified as severe. There were four serious AEs (reported in three patients), none of which resulted in death, none reported by more than one patient, and none considered related to study drug. These serious AEs were: intestinal abscess, reported in a patient during treatment with GB 12.5 µg; bladder transitional cell carcinoma stage II, reported in a patient during treatment with GB 25 µg; and enteritis infectious and acute prerenal failure, both of which were reported in a patient during treatment with GB 50 µg. There were no noticeable changes in vital signs from Day 1 to Day 7 in any treatment group.

4. Discussion

This study demonstrated that 7 days treatment with an

Table 2
Number of patients with treatment emergent AEs, SAEs, and most common AEs (occurring in at least 2 patients in any treatment group) (safety population).

Patients, n (%)	GB 12.5 μg BID + BDP/FF (N = 175)	GB 25 μg BID + BDP/FF (N = 175)	GB 50 μg BID + BDP/FF (N = 175)	BDP/FF (N = 172)	Overall (N = 178)
Any treatment-emergent AE	13 (7.4)	10 (5.7)	14 (8.0)	19 (11.0)	47 (26.4)
Nasopharyngitis	0	0	0	2 (1.2)	2 (1.1)
Oral herpes	2 (1.1)	0	0	0	2 (1.1)
Headache	1 (0.6)	0	2 (1.1)	4 (2.3)	7 (3.9)
Fatigue	0	0	2 (1.1)	1 (0.6)	3 (1.7)
Blood bilirubin increased	0	0	0	3 (1.7)	3 (1.7)
Patients with study drug permanently discontinued due to a treatment-emergent AE	1 (0.6)	1 (0.6)	1 (0.6)	0	3 (1.7)
Any treatment-emergent SAE	1 (0.6)	1 (0.6)	1 (0.6)	0	3 (1.7)

extrafine GB pMDI added to extrafine BDP/FF caused dose-dependent improvements in lung function. The primary endpoint analysis of FEV_1 AUC_{0-12h} on Day 7 showed that both 25 and 50 μg BID doses resulted in lung function improvements ≥100 mL. An FEV_1 change of ≥100 mL has been described as one that patients can perceive, and so is considered clinically relevant [10]. Although strictly speaking this refers to a single FEV_1 assessment (rather than the averaged value that the AUC represents), we believe that this suggests that the 25 μg BID dose may meet the criteria for the minimally effective dose. The results for the other spirometry endpoints were consistent with the primary endpoint, in that all three GB doses resulted in statistically significant improvements in lung function when added to BDP/FF, with evidence of a dose-response.

The primary and secondary endpoint data for FEV_1 AUC_{0-12h} and trough values on Days 1 and 7 (Figs. 2–4) all show a numerical dose-response relationship, with 12.5 μg BID having the lowest numerical effect and 50 μg BID having the highest numerical effect. The differences between 12.5 and 25 μg BID were not consistently statistically significant, but it should be noted that the study was not sufficiently powered or designed to detect smaller differences between doses, but was powered to detect an 80 mL improvement versus BDP/FF alone. For the primary endpoint (FEV_1 AUC_{0-12h} on Day 7), 12.5 μg BID failed to meet the 100 mL threshold [10]. Overall, therefore, the results presented here suggest that the effects of 12.5 μg BID fall below the clinically relevant threshold, while higher doses are more likely to be effective in clinical practice.

The primary endpoint results of the current study are consistent with those of a previous crossover study in COPD patients, which compared the effects of 'triple therapy' in the form of fluticasone propionate/salmeterol 500/50 μg BID plus tiotropium 18 μg once daily on lung function with that of fluticasone propionate/salmeterol or tiotropium bromide [11]. After 14 days, the difference in FEV_1 between the triple therapy and fluticasone propionate/salmeterol was 90 mL at 2 h post-dose and 100 mL at 4 h (both $p < 0.05$), with a difference in predose (trough) FEV_1 of 110 mL. The results are also consistent with a 12-week study in which the LAMA umeclidinium was added to the ICS/LABA FDC fluticasone fumarate/vilanterol [12]. At Day 85 trough FEV_1 was increased by 122–124 mL by the addition of umeclidinium 62.5 μg to fluticasone fumarate/vilanterol 100/25 μg.

This study examined the benefits of inhaled GB in the context of triple therapy compared with dual ICS/LABA therapy, with patients being 'stepped up' from ICS/LABA (in the run-in to each treatment period) to ICS/LABA plus LAMA. This also addresses one of the shortcomings of the designs of typical COPD clinical trials – namely the recruitment of heterogeneous patient populations into clinical trials. For example, many large trials of ICS have enrolled patients using ICS and those not using ICS [13,14]. Furthermore, in these other trials ICS were stopped during the run in, before randomisation to active treatment including ICS or placebo. All of the patients recruited into our study were taking ICS/LABA before screening (97.8% were receiving ICS/LABA on entry, with the remaining 2.2% receiving ICS/LABA/LAMA), and continued on a standardised ICS/LABA regimen during the study so removing such heterogeneity, making the evaluation of LAMA efficacy more clinically representative and the potential confounding of the conclusions drawn.

ICS/LABA treatment is one of the two most common routes to triple inhaled therapy – the other being the addition of an ICS/LABA combination to LAMA. In this context, we believe that the recruited population is representative of those who could receive triple therapy in real life. However, this was a short-term crossover study designed to evaluate the dose-response to GB, so patients were not required to be symptomatic or to have a history of frequent exacerbations – either of which would be the rationale for increasing therapy from ICS/LABA to triple inhaled therapy in real life.

A characteristic feature of COPD is hyperinflation, which is due to air trapping that results from expiratory flow limitation [15]. Hyperinflation can occur during exercise (dynamic hyperinflation) or at rest, and, together with peripheral muscle weakness, can result in activity limitation (or avoidance) that impacts overall quality of life [15]. Long-acting bronchodilators improve lung emptying, thereby reducing hyperinflation, with a combination of a LAMA and a LABA having been shown to be more effective in this regard than bronchodilator monotherapy [16]. In this context, the two volume measures included in this study (FVC and IC) provide further support for the benefit of adding a LAMA to ICS/LABA therapy.

The crossover design of the study meant that washout periods were required between the treatment periods (during which patients continued only with BDP/FF). The duration of these washout periods was determined by the plasma elimination half-life of GB; we observed similar baseline (pre-treatment) mean FEV_1 values at the start of each treatment period, confirming a lack of period or carry-over effect. The duration of treatment (7 days) was considered sufficient for the lung function parameters to be assessed accurately. This study design is not appropriate, however, for the assessment of symptoms which require a longer treatment period.

Since this study set out to investigate dose-response from a relatively small sample size, we excluded patients with limited or no bronchial reversibility to improve the chances of observing a dose-response. Such inclusion criteria are common in short term crossover studies of bronchodilators in COPD [17,18]. The potential criticism of using a reversibility threshold for inclusion is that the study is biased towards reversible COPD patients. This would certainly be the case when using a threshold such as 200 mL. We set a lower (arbitrary) value of 60 mL in order to avoid this issue, but at the same time also avoiding recruiting patients with very low (<60 mL) bronchodilator responses where it would be difficult to study dose response effects.

Although another dry-powder formulation of GB is approved for

once-daily dosing (at a dose of 50 μg once daily), it has been shown that GB can be administered twice daily [19] – the dosing regimen used for the formulation in the current study. Given the twice daily dosing regimen of BDP/FF, in the same device as used for GB in the current study, a logical future development is the co-formulation of BDP/FF and GB in the same inhaler. This would translate into advantages to patients, who, in order to receive LABA plus LAMA plus ICS therapy, currently have to use two different inhaler devices. Furthermore, although this study is not long enough to draw firm conclusions on the safety profile of GB, the relatively low number of AEs and the lack of relationship between AE incidence and GB dose is reassuring.

In conclusion, for patients already on BDP/FF, this study shows the potential benefits on lung function of stepping up to triple therapy through the addition of extrafine GB delivered via pMDI administered twice daily. The results suggest that GB 25 μg BID may meet the criteria for the minimally effective dose, although additional studies are required to confirm this. The symptomatic and longer-term clinical benefits of this approach are being investigated in long-term studies.

Conflicts of interest

DS has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from various pharmaceutical companies including Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GlaxoSmithKline, Glenmark, Johnson and Johnson, Merck, NAPP, Novartis, Pfizer, Skypharma, Takeda, Teva, Therevance and Verona.

WS-B, MH and ZS have no relevant conflicts of interest.

GC, AM, FB-G and SP are employees of Chiesi, the study sponsor.

Acknowledgements and funding

This study was funded by Chiesi Farmaceutici S.p.A. The sponsor was responsible for the study design, the analysis and interpretation of the data and the writing of the study report, and oversaw the collection of data. All authors were jointly responsible for the decision to submit the article for publication.

The authors would like to thank the investigators and patients at the investigative sites for their support of this study.

Writing support was provided by David Young of Young Medical Communications and Consulting Ltd. This support was funded by Chiesi Farmaceutici S.p.A.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.03.018.

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